

complacent. We obviously had not recognised the perception that we represented the regime and were its mouthpiece; that the situation was more sensitive than we had realised; that feelings of hurt and anguish ran deep; that we had in fact been resigned to accepting an atrocious situation. I apologised for this complacency, for the loss of dignity our colleagues had suffered for so long, and for all our errors of omission, and expressed the heartfelt hope that we could look forward to a future of reconciliation and join hands in peace and friendship. It is with very great joy that in the subsequent two years I have seen such forgiveness and willingness to put the past aside, both in medical circles and in our country as a whole.

J. Adno

Suite 6, Park Lane Clinic
Parktown
Johannesburg

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The effectiveness and cost of exogenous pulmonary surfactant replacement therapy

To the Editor: The articles¹⁻⁴ recently published on surfactant replacement therapy (SRT) in the treatment of newborn infants with hyaline membrane disease (HMD) being ventilated in a country with limited health resources are both timely and urgently needed. Surfactant, being an expensive drug, needs to be administered in the most cost-effective fashion and for this reason research guidelines for its administration in South Africa are needed. We are concerned that the discussions of this series of articles do not sufficiently emphasise their limitations, as well as the enormous impact of SRT on survival rates and other neonatal morbidities in newborn infants ventilated with HMD. It has been stated that SRT is one of the many recent triumphs of medical science.⁵ The efficacy of both natural and synthetic exogenous surfactant for prevention and treatment of HMD has been confirmed in several large randomised clinical trials.⁶ The impact on mortality in the USA since its release in 1990 has been dramatic, with decreases of 15% in overall neonatal mortality and as high as 50% in high-risk groups such as infants delivered at less than 29 weeks' gestation or weighing less than 1 200 g. The costs saved are also considerable, with Soll *et al.*⁹ reporting a reduction of US\$ 3 319 per 28-day survivor for babies who received exogenous SRT (natural surfactant) versus sham-air. Calculations that take into account both the offset of savings incurred by increasing numbers of very-low-birth-weight infants and the higher costs for babies who survived instead of dying, suggest that the USA saved an estimated \$90 million (1985 - 1990).⁹ Like the local studies, these studies do not show a net reduction in the total number of days of hospitalisation.^{2,4}

Since these calculations might not be applicable to a country with limited financial resources, their use in South Africa requires investigation. The indications investigated by Ballot *et al.*² to prevent the unnecessary use of SRT stimulate further debate. In the group of neonates with severe HMD (Table III, group 2) where SRT was withheld for

longer than 6 hours, the mortality rate was an unacceptable 38% (5/13). This did not significantly differ from the mortality rate (22%, 2/9) experienced in the group of babies (group 1) who received early SRT. This lack of difference is probably due to a type 2 statistical error (too few babies enrolled). In neonates with severe HMD the delayed administration led to a 15% reduction in SRT use. The authors acknowledge that this is not justified and that SRT should be administered early to neonates with severe HMD. The study design did not allow for the inclusion of a group of neonates with moderate HMD (fractional inspired oxygen concentration (FiO₂) < 0.75) who received SRT within 6 hours of birth. We consider that this is a major limitation, since we do not know whether there would have been a reduction in the morbidity (duration of ventilation, pneumothorax rate or length of hospitalisation) of these neonates when compared with the neonates who received SRT after 6 hours. These data are essential for formulating guidelines and calculating costs.

A subsequent article by Davies *et al.*⁴ assessed and compared the cost and effectiveness of a policy of delayed surfactant replacement therapy (SRT) in a group of babies with HMD versus that of a historical control group using guidelines similar to those developed by Ballot *et al.*² The authors show that SRT (Survanta; Abbott) led to an increase in the total cost of treating a baby ventilated for HMD. A critical review of these published data is essential, as they could have far-reaching consequences for the effective care of neonates with HMD in southern Africa.

The authors studied ventilated babies, selected to receive SRT according to their initial oxygen requirements (arterial/alveolar oxygen ratio), and compared them with a retrospective group of babies ventilated at their institution before the introduction of SRT. As the authors report, there are significant demographic differences between the SRT and control groups. The babies in the SRT group were of lower birth weight, received less antenatal care (72% v. 15% unbooked) and included more black infants (74% v. 28%). The infants in the SRT group probably had more severe disease, as reflected by the fact that more of them needed inotropic support and paralysis, although no recognised objective evidence of the severity of the HMD such as arterial/alveolar oxygen ratio for the two groups is presented.

We want to emphasise firstly the differences between the SRT and control groups and secondly the limitations of the indications used for the administration of SRT. We believe that the conclusions drawn from the data should be interpreted with caution. It is not clear to us why the use of SRT did not lead to a reduction in mortality and morbidity, as has been universally reported. Clarification for this could be found in a faulty study design or in the neonates selected to receive SRT. Ballot *et al.*² included 1 baby with a congenital heart lesion, 4 with presumed bacterial pneumonia, and, as pointed out in the article, an unknown number of severely asphyxiated babies.

To date more than 35 randomised controlled trials on SRT have now been conducted involving more than 6 000 babies and have demonstrated a consistent 40% reduction in the odds of neonatal death after surfactant treatment.⁶

Treatment of established HMD offers the advantage of limiting the number of individuals treated to only those babies with definite HMD. The most appropriate time to treat manifest (rescue) HMD seems to be within the first 6 hours after birth. Thereafter various factors may be operative in

inactivating the surface properties of exogenous surfactant. Lang *et al.*¹⁰ found in stepwise discriminant analysis that rescue therapy with surfactant before 4 hours of age was associated with improved outcome compared with that in infants rescued at a later stage.

Respiratory distress syndrome is a complex problem not solely attributed to surfactant deficiency. In addition, mortality often results from causes other than respiratory failure, limiting the impact on overall mortality. The significant differences observed in mortality rates between severe and mild/moderate HMD groups in the study of Ballot *et al.*² could be accounted for by the inclusion of babies with diseases other than HMD.

There is now irrefutable evidence that the administration of steroids to women expected to deliver preterm reduces the incidence of HMD. It was estimated in one controlled trial of antenatal steroids that prophylaxis more than halved subsequent hospital costs in the group that had received the drugs.¹¹ This is a more cost-effective approach than administering SRT for HMD. In the article by Davis *et al.*⁴ only 5% of mothers received antenatal steroids. The greatest saving in the administration of SRT would be achieved by ensuring that all mothers in premature labour (< 34 weeks) receive antenatal steroids.

Until controlled trials are conducted in South Africa to address some of the limitations highlighted by the series of publications from the University of the Witwatersrand,¹⁻⁴ it is our opinion that this form of life-saving and efficacious therapy should not be withheld from neonates with moderate and severe HMD.

J. Smith

C. Pieper

R. P. Gie

Department of Paediatrics and Child Health
University of Stellenbosch
Tygerberg, W. Cape

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Professor Rothberg and Drs Davies and Ballot reply: The response from Tygerberg characterises the philosophical debate which has taken place between that neonatal unit and the Johannesburg unit since the advent of surfactant replacement therapy. The positions can be summarised as follows: Tygerberg promotes aggressive intervention, using survival as a major indicator of success; Johannesburg promotes targeted intervention, keeping in mind the consequences of salvaging additional babies within a system which cannot cope with a pre-existing burden.

Smith *et al.* are correct in their analyses of the predominantly North American experience. However, they do not emphasise the point that the major impact has been in those babies who are usually not ventilated in this country because of resource constraints. Several studies and analyses have shown dramatic results in babies weighing between 500 and 1 000 g.^{1,2} In fact, the reference cited by Tygerberg to support their argument³ shows quite clearly that the surfactant-related effect on mortality is inversely related to birth weight; while there is a significant difference between pre- and post-surfactant mortality rates for babies weighing less than 1 000 g (41,5% v. 34,7%; $P < 0,01$), there is no difference for babies weighing 1 000 g or more (9,9% v. 8,3%; $P = 0,2$). As Smith *et al.* well know, most academic units in South Africa will not routinely ventilate babies weighing less than 1 000 g.

The paper by Schwartz *et al.*³ also includes an interesting comment under 'Methods', i.e. that the 14 units underwent a 25% increase in size during the period under review, although the number of births did not change. This requirement to 'upscale' represents the cost of additional survivors, and, in the context of the Johannesburg academic experience, would represent a cost that could not currently be considered. In similar vein, Smith⁴ recently presented data showing that providing CPAP to those neonates who 'don't qualify for ventilation' increases their chance of survival by some 300%. Again, the question is not one of viability or availability of ventilators for this group of tiny neonates; as always it is one of being able to accept the consequences of 'unrationed' care, in particular physically being able to accommodate more babies.

While the authors of the series of papers on surfactant replacement therapy⁵⁻⁸ will continue to defend their general argument against the Tygerberg plea for unrestricted use, they do acknowledge an important point made by the Tygerberg group. The Johannesburg studies took a historic experience of 87% survival in surfactant-deficient infants and asked whether it was necessary to treat 100% of neonates with surfactant to enhance an already acceptable survival figure. The group decided on a strategy to identify only those who 'qualified', and ended up treating only 59% of infants. The Tygerberg group rightly points out that an ideal next step would be a study to compare the 41% currently denied surfactant with a similar group given surfactant within the first few hours of life. Only then would it really be possible to comment on the cost or cost-benefit of the Johannesburg protocol, but in the interim it would seem that some savings are achieved by not treating all eligible infants, and outcome is not significantly compromised.

In terms of any savings related to surfactant use, it must be recognised that the basis for calculation in the South African academic context is solely 'global cost per bed day'.⁹ Therefore, if there are only marginal differences in the duration of stay at the various levels of care,⁹ surfactant use will obviously represent an additional cost. If, on the other hand, one were able accurately to assess specific, itemised differences in resource utilisation for groups pre- and post surfactant as was done in the US review,³ savings might well emerge. Unfortunately such analysis remains problematic in the context of our public hospitals.

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Containing costs

To the Editor: At a recent meeting with the National Pathologists Group earlier this year a few issues were raised. Firstly, they complain that most request forms are received without any clinical details. Were these included, they could help the pathologist to consider the relevance of the tests requested and possibly advise the clinician accordingly.

The second point raised was whether doctors knew the costs of any tests they requested.

Both these items are of importance in the endeavour to contain costs, the main factor that will enable private care to continue.

E. D. Sonnenfeld

Medical Adviser

Medscheme (Pty) Ltd
300 Kent Avenue
Randburg, Gauteng

The influence of the tuberculosis epidemic on ICU resources

To the Editor: Over the past decade there has been a world-wide increase in the incidence of tuberculosis. Nowhere has this been greater than in the Western Cape, where the incidence of tuberculosis is 472/100 000 workers in industry and the disease causes 7% of deaths between the ages of 7 and 60 years.^{1,2} The number of patients with pulmonary or disseminated tuberculosis admitted to the respiratory intensive care unit at Groote Schuur Hospital has increased dramatically over the past 10 years, with 164 patients being admitted, and during 1993 and 1994 tuberculosis contributed to 6% of admission (Fig. 1.) The mortality in these patients (29%) is remarkable considering the severity of this slowly responding infective disease; unfortunately we are as yet unable to predict which patients will do well, so as to facilitate appropriate triage. Of interest is that this increase is not a result of HIV infection or multidrug-resistant tuberculosis, as only 1 patient was HIV-positive, and one had multiresistant disease.³ If this increase continues the numbers could be predicted to double in the next 3 - 5 years; however, as HIV infection influences this trend, even greater numbers could be expected.⁴ While this increase will place a considerable burden on community health services, there will be an inevitable influence on other specialised areas. Of great

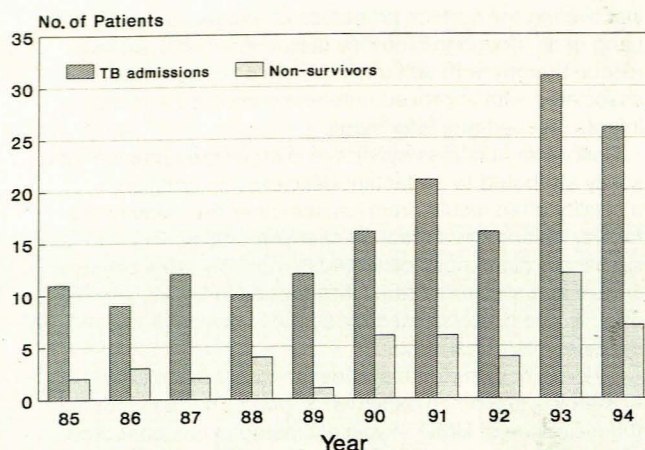


Fig. 1. Annual incidence and outcome in patients with pulmonary or disseminated tuberculosis requiring care in the respiratory ICU at Groote Schuur Hospital.

concern will be the increasing demands on already limited ICU resources, and the considerable health risk to staff.⁵ The cost of treating these patients may be estimated from a previous cost analysis in this unit at R20 388 per survivor.⁶ Additional expenditure will also be needed to help prevent the disease from spreading from patients requiring mechanical ventilation to staff and other patients.⁷

If these increased ICU needs are not met increasing triage of patients will be necessary, and this will inevitably result in some patients who would only survive with intensive care treatment not being given this therapy.

P. D. Potgieter

Intensive Care Unit
Groote Schuur Hospital
Cape Town

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Financial support for SAMJ research, 1994

To the Editor: Several national and international initiatives aimed at setting priorities for health and medical research have highlighted the need for accurate data on the sources of funding used for research. Such data are important for several reasons: (i) priority-setting processes need to involve funders if they are to be successful; and (ii) certain funding sources may adversely influence the medium- and long-term direction and impact of research.

In South Africa, the ministerially appointed Committee into Essential National Health Research, in attempting to document funding sources, identified the need for a more thorough review of funding sources to be undertaken. This brief report contributes to that need.